REMARKS

Claims 65-72 are pending in this application; claims 65-72 are rejected. Claims 67 and 71 are cancelled. Claims 65 and 69 are amended to incorporate the language from dependent claims 67 and 71, respectively. Claims 65 and 69 are further amended to point out that the nucleic acid ligand is administered to a mammal. This amendment is supported by the Applicants' specification at, for example, paragraphs [0074]-[0082]. Applicants believe that no new material has been added.

All references to the specification refer to the published application, U.S. 2004/0072234. Applicants respectfully request reconsideration of the application as follows:

I. Sequence Rule Compliance

The Examiner requests that sequences found in the Figures and specification be added to the SEQUENCE LISTING. Submitted concurrently with this amendment is an electronic copy of the revised SEQUENCE LISTING for the above-identified application submitted under 37 C.F.R. § 1.821(e) and a Statement to Support Filing and Submission. Applicants respectfully request that the electronic copy of the SEQUENCE LISTING be entered into the application. The electronic copy contains no new matter (37 C.F.R. § 1.821 (g)). Support for the electronic SEQUENCE LISTING is found in the application as filed and in the original SEQUENCE LISTING of record.

Applicants do not believe a paper copy is required at this time. If the Examiner further requires a paper copy, please inform the undersigned.

II. Priority

The Examiner accords the effective filing date for the present application as June 5, 1996, asserting that the applications filed prior to PCT/US96/9455 fail to disclose the instantly claimed invention. Applicants respectfully point out that adequate support and enablement as required by 35 U.S.C. § 112, first paragraph, is provided at least by the disclosures of U.S. Patent Nos. 5,766,853, 6,001,988, and 5,780,228. Each of these patents has a filing date of June 7, 1995.

Each of the '853, '988, and '228 disclosures are nearly identical to the others, so citations will be provided only to the '853 patent. Adequate support and enablement can be found in the '853 patent at, for example: column 2, line 20 through column 4, line 6 describing the use of the nucleic acid aptamers as therapeutics; column 10, lines 51-58 describing the characteristics desirable for use as pharmaceuticals; Example 7 (beginning at column 20) describing RNA

ligands to L-selectin; Examples 8-12 (beginning at column 24) describing RNA ligands to LS-RG, including specificity, binding to PBMCs, binding to Sialyl Lewis^x, and secondary structure; Examples 13-17 describing ssDNA ligands to L-selectin including affinities, selectivity, cell binding studies, and secondary structure; Example 18 describing how RNA ligands to E-selectin can be obtained; Example 19 describing how RNA ligands to P-selectin can be obtained; Tables VIIa and VIIb demonstrating use of SELEX to obtain RNA ligands to L-selectin; Table VIII listing sequences of RNA ligands selected for binding to L-selectin; Tables IX and X demonstrating dissociation constants and specificity of selected RNA ligands to L-selectin; Table XI demonstrating use of SELEX to obtain ssDNA ligands to LS-Rg; Table XII listing sequences of ssDNA ligands selected for binding to L-selectin, including SEQ ID NO: 172 which is the same as SEQ ID NO: 185 of the present application; and Tables XIII and XIV demonstrating dissociation constants and specificities of selected ssDNA ligands to L-selectin. The final paragraph of column 32 concludes with the observation that the similarity of L-selectin and P-selectin's binding properties assures the success of the experimental procedures in isolating nucleic acid ligands to P-selectin. Thus, as adequate support is found in these earlier applications, Applicants respectfully request accordance of the June 7, 1995 priority date for the present application.

III. Information Disclosure Statement

The Examiner requests that the IDS submitted on January 7, 2004 and January 28, 2005 be corrected to reflect appropriate titles for non-patent literature. Enclosed herein are corrected versions of both documents.

IV. Objections to the Specification

The Examiner objects to the abstract of the disclosure for lacking statements directed to the claimed invention. A replacement abstract is provided herein.

The Examiner objects to various other aspects of Applicants' specification. All references to the specification in this amendment refer to Application Publication No. 2004/0072234.

The Examiner objects to the specification and Figures for containing sequences lacking SEQ ID NOs. Replacement paragraphs with proper SEQ ID NOs are provided above for those (1) paragraphs containing sequences and (2) paragraphs referring to Figures with sequences.

Applicants believe that no new matter is added by these amendments. The amendments are supported by the original text of the respective paragraphs.

The Examiner objects to typographical errors found in the title of Table 20. Applicants respectfully point out that the title for Table 20 found on page 46, paragraph [0034] of the published application appears to be correct.

Other minor amendments have been made to the specification to correct obvious typographical errors and to update prior application data. These amendments to the specification do not add any new matter to the application or affect the claimed invention.

V. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

The Examiner rejects claims 65-72 under 35 U.S.C. § 112, first paragraph as non-enabled by the specification. A patent application must be written such that one skilled in the art to which it pertains is enabled to make and use the invention without undue experimentation (*In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)). A specification is presumed enabling (*In re Marzocchi*, 169 U.S.P.Q. 267, 369 (C.C.P.A. 1971)), and may be so even though experimentation is required (*U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988)). The fact that experimentation may be complex does not necessarily make it undue if such experimentation is typically performed in the art (*In re Wands*, 858 F.2d at 737). The test is not whether any experimentation is necessary, but whether necessary experimentation is undue (*In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976). It is not necessary to "enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect" (*CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003)).

Factors to be considered in making a determination of whether undue experimentation is required include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure (*In re Wands*, 858 F.2d at 737).

The present claims are directed to methods for (1) treating lectin-mediated platelet disorders and (2) treating lectin-mediated inflammation or lymphocyte tracking disorders, the methods comprise administering a pharmaceutically effective amount of a nucleic acid to a lectin. The Examiner asserts that one of ordinary skill in the art would not have known how to

use the nucleic acid ligands as therapeutics nor determine whether the ligand would function as a pharmaceutical agent to treat a particular disorder without "appropriate *in vivo* evidence". The Examiner cites several articles to demonstrate the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, and the level of predictability of the invention.

Stull and Szoka (*Pharmaceutical Research*, 1995, Vol. 12, No. 4, pages 465-483) provide insight into the state of the art in 1994 and 1995. Stull and Szoka report four instances of nucleic acid aptamers exhibiting biological effects *in vitro*, one of which also demonstrated *in vivo* activity. In addition, Stull and Szoka discuss the obstacles to the use of nucleic acid aptamers *in vivo* and *in vitro*.

Stull and Szoka point out that chemical modifications and/or introduction of hairpin forming sequences in nucleic acid aptamers improve aptamer stability in biological systems (page 476, column 1). Applicants addressed this issue in their disclosure at, for example, paragraph [0060] where they describe chemical modification and/or nucleotide substitution as useful techniques for improving *in vivo* stability or to enhance or mediate delivery of the aptamer. Applicants demonstrate secondary structure in the form of hairpin forming sequences for L-selectin 2'NH_2 RNA ligands (Example 12 and FIG. 7), family 1 ssDNA ligands to L-selectin (Example 17 and FIG. 12), 2'-F RNA ligands to L-selectin (Example 25 and FIG. 15), and 2'-F RNA ligands to P-selectin (Example 31 and FIG. 16). Applicants also performed 2'-O-methyl substitution experiments on 2'F pyrimidine RNA ligands to P-selectin to decrease susceptibility of the ligands to nuclease digestion (Example 27F and 34).

Stull and Szoka also point out that the affinity of a nucleic acid drug for its target is a crucial parameter (page 476, column 1). Applicants have addressed this issue as well, providing a proprietary method for developing aptamers with high affinity for a particular target (paragraphs [0054]-[0058]), a method believed by Applicants to be an unprecedented achievement in the field of nucleic acid research (paragraph [0063]). Applicants' method of SELEX produced ligands with pM and nM affinities to various lectins, including RNA ligands to WGA (Table 3 and Example 2C), 2'NH_2 RNA ligands to L-selectin (Table 9 and Example 8C), ssDNA ligands to L-selectin (Table 13 and Example 14C), 2'F ligands to L-selectin (Table 17 and Example 23C), 2'F RNA ligands to P-selectin (Table 20 and Example 28), and 2'NH_2 RNA ligands to P-selectin (Table 26 and Example 36C). The use of SELEX effectively mitigates unpredictability in the aptamer art.

Stull and Szoka further explain the difficulty of distributing nucleic acid aptamers to obtain biological effect. Applicants again anticipated this difficulty, and in designing their aptamers provided for, among other possibilities, lipophilic complexed nucleic acid ligands or lipophilic encapsulated ligands (*i.e.*, liposomal delivery) to enhance cellular uptake of the ligands for delivery to an intracellular target (paragraph [0060]). Applicants incorporate by reference U.S. Patent Application No. 08/434,465, now U.S. Patent No. 6,011,020 which discusses methods for preparing therapeutics comprising a nucleic acid ligand and a lipophilic compound or a non-immunogenic, high molecular weight compound (paragraph [0060], last sentence). Stull and Szoka agree that this is a useful approach, and report in Table IV on page 477 a reference demonstrating that targeted liposomal delivery of nucleic acid drugs enhances cytoplasmic delivery and prevents drug degradation (see also paragraph bridging page 477 and 478).

As the Examiner points out, Stull and Szoka's concluding paragraph indicates that drug delivery and targeting is the primary obstacle to the use of nucleic acid aptamers in a clinical setting. However, Applicants had the foresight to address these difficulties in their disclosure. Thus the state of the art was such that, at the time Applicants filed the application, one of skill in the art had available techniques for ensuring delivery of nucleic acid ligands to target molecules *in vivo*.

The Examiner maintains that "the state of the therapeutic aptamer art remains unpredictable" such that therapeutic effects of any aptamer selected through the use of SELEX could not be predicted by one of skill in the art without undue experimentation. Applicant respectfully disagrees. Applicant has conceived of and generated nucleic acid ligands that have affinity and specificity for P-selectin and L-selectin. Applicants demonstrated that these ligands are effective *in vitro* with competitive binding assays, affinity determinations, cell binding studies, lymphocyte trafficking experiments, and sialyl Lewis^x binding inhibition assays. That these ligands will have therapeutic effect *in vivo* is in fact predictable. The Examiner cites Fichou *et al.* (*TRENDS in Biotechnology*, available online October 12, 2006) to demonstrate that even now, the clinical use of aptamers is unpredictable. On page 5, column 1, second full paragraph, Fichou *et al.* discuss the use of SELEX to produce aptamers with high affinity, and aptamers that recognize both the human and animal protein of interest. In the following paragraph, they mention the advantages of aptamers, including the ability to easily modify the

aptamer backbone to prevent premature nuclease degradation and clearance, as well as the ability to improve clinical trial safety through the use of "antidotes" to the aptamers. Thus, aptamers are highly advantageous over other therapeutic compounds.

The Examiner mentions one clinical study that failed to demonstrate beneficial effects described by Fichou *et al.* at page 6, column 1, first paragraph. However, at the last sentence of that paragraph, Fichou *et al.* point out why the study failed: the target protein, E2F, includes at least eight isoforms that have antagonist effects and therefore the E2F decoy was not specific enough. This is a problem with the researchers' understanding of the target protein, not whether aptamers designed with specificity and affinity would be good therapeutics.

Fichou *et al.* mention that the main limitation of aptamers is that local administration is required to avoid impairment of proteins in untargeted organs. This is not a problem limited to aptamers, and indeed affects all developing drugs. Further, this statement strays from the issue of whether identified aptamers can predictably function as pharmaceutical agents to treat a specific disorder. Many therapeutics have side-effects; aptamers that impair proteins in untargeted organs can have side-effects as well.

Fichou *et al.* point out in their concluding paragraph that many improvements are required in delivery and *in vivo* efficiency. As described above, Applicants address these issues in the disclosure of the present application, enabling one skilled in the art to overcome the challenges and limitations in the clinical use of aptamers (paragraph [0060]).

The Examiner states that the art recognizes that having an aptamer sequence in hand does not mirror therapeutic efficacy and undue experimentation would be required for one skilled in the art to determine the therapeutic efficacy of the aptamer. Applicants have, however, demonstrated "proof of concept" with animal studies by performing the lymphocyte trafficking experiments shown in Example 13H and Example 20 using SCID mice. The mice were injected with human untreated PBMC or PBMC treated with varying concentrations of the nucleic acid ligands (NEX288, LD174T1, and NEX303), then euthanized an hour later. Tissues taken from the animals were then analyzed to determine where labelled PBMCs had accumulated. Figures 13 and 14 show the results of these experiments and demonstrate the ability of nucleic acid ligands to block trafficking.

Thus, one of ordinary skill in the art would have known at the time the application was filed how to use the claimed nucleic acid ligands as therapeutic agents and how such ligands would function as pharmaceutical agents to treat a particular disorder.

Moreover, Applicants provide sufficient guidelines throughout the specification and in the examples to enable the use of nucleic acid ligands as therapeutics. Applicants provide animal models for testing the efficacy of nucleic acid ligands in vivo, including mouse models for peritoneal inflammation, diabetes, lymphocyte tracking, glomerulonephritis, acute inflammation in human/SCID mouse chimera, and endotoxin-mediated inflammation (paragraph [0074]; see also paragraphs [0075]-[0082] for additional animal models).

Applicants describe parenteral administration of formulations containing nucleic acid ligands, and provide appropriate carriers and other excipients necessary to maintain a formulation containing the ligand (paragraph [0071]). Applicants provide means of storage for formulations containing the ligand (paragraph [0072]).

Applicants' working examples provide evidence of the ability of the nucleic acid ligands to treat lectin-mediated platelet disorder, lymphocyte tracking disorder, and lectin-mediated inflammation. Examples 7-25 show how nucleic acid ligands to L-selectin are characterized: 2'NH2 ligands to human L-selectin were tested for binding specificity to L-selectin using isolated peripheral blood mononuclear cells (Examples 7E and 10), for inhibition of LS-Rg binding to sialyl-Lewis^x (Examples 7F and 11), and for affinity and specificity to L-selectin (Exampes 8C and 9); ssDNA ligands to human L-selectin were tested for binding specificity to L-selectin using isolated human peripheral blood mononuclear cells (Examples 13E and 16), for affinity to L-selectin (Example 14C), for selectivity to L-selectin (Example 15), for ability in SCID mice to affect lymphocyte tracking to organs (Examples 13H and 20), and for inhibition of LS-Rg binding to sialyl-Lewis^x (Examples 13I and 19); 2'F RNA ligands to human L-selectin were tested for binding specificity to L-selectin using isolated peripheral blood mononuclear cells (Examples 22E and 24) and for affinity to L-selectin (Example 23C).

Likewise, Examples 26-39 show how nucleic acid ligands to P-selectin are characterized: 2'F RNA ligands to P-selectin were tested for ability to bind P-selectin using human platelet suspensions (Example 27G and 33), for ability of ligands to inhibit selectin binding to sialyl-Lewis^x (Examples 27H and 30), for affinity of ligands to P-selectin (Example 28D), and for specificity of ligands for P-selectin (Example 29); 2'-NH2 RNA ligands to human P-selectin

were tested for ability to bind P-selectin using human platelet suspensions (Examples 35 E and 38), for affinity to P-selectin (Example 36C), for specificity to P-selectin (Example 37), and for ability of ligands to inhibit selectin binding to sialyl-Lewis^x.

Furthermore, many of the Examples were performed with the nucleic acid ligand LD201T1 (represented by SEQ ID NO: 185): branched dimers of LD201T1 were synthesized and characterized by binding to human peripheral blood mononuclear cells (Example 13F); LD201T1cell binding studies were performed demonstrating that LD201T1 binds saturably and specifically to human L-selectin on lymphocytes and neutrophils (Example 16); using blocking experiments, competition experiments, and photocrosslinking experiments, LD201T1 was determined to bind to the lectin domain of L-selectin (Example 17); experiments comparing the affinity of the full length ligand with the truncated LD201T1 found no significant difference (Example 18); binding inhibition studies determined that LD201T1 competes with sialyl-Lewis^x for LS-Rg binding; and, as mentioned above, LD201T1 was formed into a dimer and tested for affinity to selectin on purified lymphocytes. Similarly, Examples were performed with the nucleic acid ligand PF-377 (represented by SEQ ID NO: 206): specificity and affinity of PF-377 is shown in Table 20; and binding inhibition studies determined that ligand PF-377 has an IC-50 of approximately 2nM with complete inhibition attained at 10 nM, demonstrating that the ligand is a functional antagonist of PS-Rg.

Thus, Applicants provide sufficient direction in the specification and in the Examples as to how to identify nucleic acid ligands with desired activity and stability. The nature of the invention and the state of the prior art are such that one of ordinary skill in the art would be able to address stability and delivery issues identified by Applicants based on the teachings in the specification and the Examples. Applicants have provided the SELEX method to mitigate the unpredictability formerly experienced by those practicing in the nucleic acid ligand field.

The Examiner asserts that the claimed methods are so broad as to encompass any nucleic acid ligand to any lectin which exhibits activity in any living organism toward any lectin. Though Applicants maintain that the claims as written are enabled by the specification, in order to expedite prosecution, claim 65 is amended to specify P-selectin as the lectin targeted by the nucleic acid ligand. Claim 69 is likewise amended to specify L-selectin as the lectin targeted by the nucleic acid ligand. Claims 65 and 69 are further amended to indicate that the nucleic acid ligand is administered to a mammal.

VI. Obviousness-Type Double-Patenting Rejection of Claims

The Examiner rejects claims 65-72 under the judicially created doctrine of obviousness-type double patenting as not patentably distinct from claims 1-2 and 4-7 of U.S. Patent No. 6,544,959. When allowable subject matter has been determined, Applicants will submit a terminal disclaimer.

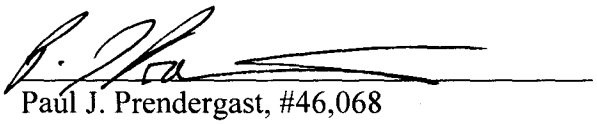
CONCLUSIONS

For the reasons set forth above, Applicant respectfully submits the claims as filed are allowable over the art of record and reconsideration and issuance of a notice of allowance are respectfully requested. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This amendment is submitted contemporaneously with a petition for a two-month extension of time in accordance with 37 C.F.R. § 1.136(a). Accordingly, please charge deposit account No. 19-5117 for a two-month extension of time fee. Applicants believe that no further fees or petitions are required. However, if any such petitions or fees are necessary, please consider this a request therefore and authorization to charge deposit account No. 19-5117 accordingly.

Respectfully submitted,

Dated: 5/23/07



Paul J. Prendergast, #46,068
Swanson & Bratschun, L.L.C.
1745 Shea Center Drive, Suite 330
Highlands Ranch, Colorado 80129
(303) 268-0066

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